40. (New) A type I polyketide synthase according to claim 39, wherein the acyl carrier protein of said loading module is naturally associated with the said first extension module.

Add c.22 Cancel original claims 1-7 and 9-15.

REMARKS

Applicants, through their undersigned attorneys, hereby traverse and request reconsideration of the requirement for restriction set forth in the Official Action dated February 4, 2002 in the above-identified patent application.

At the outset, it is noted that a shortened statutory response period of one (1) month was specified in the February 4, 2002 Official Action. The initial due date for response, therefor, was March 4, 2002. A petition for a one (1) month extension of the response period is presented with this amendment and request for reconsideration, which is being filed within the one (1) month extension period.

The February 4, 2002 Official Action includes certain suggestions by the Examiner to the effect that the comments in the International Preliminary Examination Report (IPER) from the underlying international application be taken into account in the present application and that an amendment prior to examination to address such comments would contribute to the efficient prosecution of this application.

In response to the foregoing suggestions, applicants are presenting new claims 17-40 as set forth above, entry of which is respectfully requested. Original claims 1-15 have accordingly been canceled. Claim 16 has been retained.

Correspondence between the new and original claims is as follows:

New	Original
17	1 and 2
18	3
19	4
20	5
28	6
29	7
30	13
31	9
32	10
33	11
34	12

New claims 21-27 and 35-40 are drawn to additional specific aspects of applicants' invention, support for which is provided in the present specification, as follows:

Claim	Support
21	Paragraph bridging pages 18-19
22	Page 27, lines 3-21 and Page 28, lines 10-15

23	Examples 1-5 at pages 32-43
24	Examples 6-10 at pages 43-47
25-27	Page 27, lines 7-14
35-36	Paragraph bridging pages 19-20
37	Page 18, lines 18-20
38	Page 1, lines 12-19
39	Paragraph bridging pages 22-23
40	Examples 11-15 at pages 47-53

Further with respect to the present amendments, the preamble of new claim 17 is based on the related statement bridging pages 17 and 18 of the specification, and is further limited to "type I" polyketide synthases ("PKSs").

New claim 18 includes further characterization of the polyketide synthase enzyme of the invention based on original claim 3, with clarification based on page 18 lines 14 to 17.

In converting original claim 11 to new claim 33 the wording "comprising a system" has been amended to recite "which has been transformed to contain nucleic acid".

New claim 37 refers to the production of the PKS defined in claim 18 by site-directed mutagenesis as disclosed at page 18 in lines 18 to 20 of the present specification.

New claim 38 is similar to new claim 17. It is intended to cover embodiments in which a natural PKS with a decarboxylating loading module is modified to change the starter unit supplied by the loading module. Support for new claim 38

is provided by the general description at page 1, lines 12-19 of the present specification. New claim 38 has an additional proviso to exclude the hybrid PKS prepared by the Kuhstoss et al. publication, discussed at page 12 from line 5 of the present specification. As explained, the authors of this publication were entirely in the dark about the nature of the loading module they were dealing with. Consequently, this publication does not render claim 38 unpatentable.

New claim 39 primarily defines the loading module in terms based on the paragraph bridging pages 22 and 23 of the present specification. The term "KSq" is replaced by "(decarbox)", which is defined in terms based on page 18 lines 12 to 14 and 21 to 23, and the middle paragraph on page 23.

Considering first the patentability issues purportedly arising from the IPER, the objection in section 2.2 of the IPER need not be addressed, as there is now no claim corresponding to original claim 14.

In section 2.3, the IPER indicates that the subject matter of original claims 1 to 13 "does not solve the problem posed by the present invention". It is respectfully submitted that (1) the "problem" is incorrectly identified in the IPER; and (2) in any case, the statement that the subject matter of the original claims did not solve it is erroneous.

The principal object of the present invention is much more than simply avoiding the formation of mixtures of polyketides with acetate and propionate starter units. The

present invention results from the discovery that there are loading modules which operate in a previously unsuspected way (involving decarboxylation). The present invention enables the exploitation of this discovery in many ways. It provides further methods for preparing novel polyketides with altered starter units (see top of page 1 lines 12 to 17, and page 17 line 19 to page 18 line 9).

It makes it possible to alter the specificity of a loading module without substituting an entire new loading module (see for example page 22 line 23 to page 23 line 8).

It provides new ways to introduce greater structural diversity at the starter position by taking advantage of the range of unusual side-chains specified by AT units from extender modules. The present invention shows that these can be incorporated in starter modules. (See for example page 7 lines 3 to 15).

Applicants' discovery also makes it possible to prepare both existing and novel polyketides with reduced levels of by-products, as noted by the Examiner.

The methods of the invention also enable the preparation of type II aromatic polyketides with reduced levels of by-products.

The present claim amendments endeavor to bring the claims more into line with this assessment of the "problem" solved by the invention. However, looking at original claim 1 and the objection set forth in section 2.3 of the IPER, the claim

defines a system which uses the newly-discovered type of loading module in a way that is novel and will provide greater purity of products than was obtainable by prior art techniques. The claim defines subject matter which is novel and useful, and which is not affected by the recitation of "substantially" in the second line of the claim.

Section 2.4 of the IPER refers to documents D1, D2 and D3. These documents are much less relevant than suggested in the IPER. According to the IPER, each of documents D1 to D3 discloses "the loading of malonyl followed by decarboxylation". This appears to be based in part on a misreading of D1. The authors did observe decarboxylation, but they concluded that this was an artefact, and does not occur naturally. As stated on page 40, first column: "the decarboxylation of the ACP-bound malonate could be catalysed by a residue of the holo-ACP that only becomes accessible after partial proteolytic cleavage" (lines 11 to 15). Further down that column it is stated: "These experiments provide firm evidence that, under certain conditions, that is partial denaturation of the ACP...decarboxylation of a malonyl moiety...can be observed. This decarboxylation does not occur when malonyl ACP is fully denatured, nor when it retains its fully native structure" (final eight lines).

D2 and D3 are both publications of the research group of Dr. Khosla. These appear to disclose the loading of malonate, followed by decarboxylation, by ACP in extension modules. However, these observations are almost certainly in error. What

is more likely to have occurred was direct loading of propionate, due to the small amounts of propionate which are always present in commercial methylmalonyl CoA samples. The suggestion in D2 that KS I acts as a decarboxylase to prime itself with starter units has been rigorously disproved by Weissman et al. as explained in the present specification at page 14, lines 8 to 15; and by Pereda et al., as discussed in applicants' specification at page 13, second paragraph.

The disclosure in the present application that a particular, previously unrecognized, class of loading modules recruit malonate or substituted malonate units and then effect carboxylation to generate monocarboxylic acid starter units was completely novel and unexpected at the filing date of the present application. Whereas it was known that extension modules could do this, it was believed that loading modules recruited only monocarboxylic acids (see for example reviews by Khosla, 1997, *Chem. Rev.*, 97, 2577-2590, and Katz, 1997, *Chem. Rev.*, 97, 2557-2575).

The IPER also observed that some of the claims defined "a result to be achieved". It is respectfully submitted that this is plainly incorrect. The present invention results from the discovery that there are special types of loading module that have a decarboxylating mode of action, and provides particular uses for these loading modules. Anyone who makes such use of this special type of loading module is getting the benefit of the invention. Now that the present inventors have made it known

that those modules exist and can be put to practical use, it is a routine matter to arrive at further examples.

Turning attention to the restriction requirement in this case, this requirement is plainly improper for failure to comply with the relevant provisions of the Manual of Patent Examining Procedure (M.P.E.P.) pertaining to unity of invention determinations.

The present application was filed under 35 U.S.C. §371 as a U.S. national stage application under the Patent Cooperation Treaty.

As stated in 1893.03(d) of the M.P.E.P.:

> Examiners are reminded that unity of invention (not restriction) practice is applicable in international applications (both Chapter I and II) and in national stage (filed under 35 U.S.C. 371) applications...
>
> The principles of unity of invention are used to determine the types of claimed subject matter and the combinations of claims to different categories of invention that are permitted to be included in a single international or national stage patent application. The basic principle is that an application should relate to only one invention or, if there is more than one invention, that applicant would have a right to include in a single application only those inventions which are so linked as to form a single general inventive concept.
>
> A group of inventions is considered linked to form a single general inventive concept where there is a technical relationship among the inventions that involves at least one common or corresponding special technical feature. The expression special technical features is defined as meaning those technical features that define the contribution which each

> claimed invention, considered as a whole, makes over the prior art.... Note also examples 1-17 of Annex B Part 2 of the PCT Administrative Instructions as amended 01 July 1992 contained in Appendix AI of the M.P.E.P.

Example 17 of Annex B Part 2 of the above cited Administrative Instructions unequivocally states that a protein and the DNA sequence encoding it exhibit "corresponding special technical features" and, therefore, satisfy the PCT's unity of inventive requirement.

Accordingly, in the present case, original claims 1-7, 13 and 16, on the one hand, and claims 9-11 on the other hand, cannot properly be characterized as lacking unity of invention. The same is true of original claim 12, which is directed to producing a polyketide using the transformed organism of claim 11. It is noteworthy in this regard that there was no lack of unity objection during the international stage of this application. Rather, the subject matter of all of the original claims was treated as a single inventive concept.

As the February 4, 2002 Official Action fails to comply with established United States Patent and Trademark Office practice in requiring restriction, it is respectfully submitted that this requirement should be reconsidered and withdrawn.

In order to be fully responsive to the above-mentioned requirement, applicants hereby elect the subject matter of Group I, i.e. claims 1-7, 13 (now claims 17, 20 and 28-30) and 16 for examination in this application.

Applicants hereby reserve the right to file one or more continuing applications, as provided in 35 U.S.C. §120, on the subject matter of any claims finally held withdrawn from consideration in this application.

Early and favorable action on the merits of this application is respectfully requested.

Respectfully submitted,

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